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Prediction of antioxidant capacity, age, and sex on sleep impairment in patients with amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by high levels of inflammation and oxidative stress, predominantly affecting males, particularly those between the ages of 50 and 65 years. It is characterised by progressive loss of motor neurones, leading to both motor and non-motor symptoms, such as sleep impairment, diagnosed in most patients, which adversely affects their quality of life. Therefore, this study aimed to determine the predictive role of antioxidant capacity, psychological distress, age, and sex on sleep impairment in an adult population of patients with ALS. A descriptive, quantitative, cross-sectional study was conducted using a sample of 74 patients diagnosed with bulbar or spinal ALS. To assess sleep disturbances in these patients, the Pittsburgh sleep quality index (PSQI), epworth sleepiness scale (ESS), and Insomnia severity index were used. Additionally, plasma antioxidant capacity was analysed using the total antioxidant capacity (TEAC), Cupric Ion reducing antioxidant capacity (CUPRAC), and ferric reducing power (FRAP). Anxiety and depression measures were used to measure psychological distress. Men exhibited a higher antioxidant status (lower oxidative stress) than women, and higher antioxidant capacity was associated with fewer sleep impairments (β = −0.43). Psychological distress may increase sleep impairment (β = −0.26). Furthermore, older individuals experienced less sleep impairment (β = −0.27), while sex had minimal influence on sleep deterioration, although it appears that men had fewer disturbances (β = −0.12). Having a higher antioxidant status, lower psychological distress, being male, and being older seem to act as predictors of reduced sleep impairment in ALS. Specifically, these four predictors account for 32% of sleep deterioration.

Clínical trial registration: The present descriptive, quantitative, cross-sectional study was part of a clinical trial involving ALS patients, registered under the number NCT04654689 (https://clinicaltrials.gov/study/NCT04654689#wrapper).

Keywords ALS, Sleep impairment, Oxidative stress, Psychological distress, Age, Sex

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that predominantly affects males[1] and mainly occurs between the ages of 50 and 65 years[2]. It is characterised by progressive loss of motor neurons in the brain and spinal cord, with respiratory complications being the most common cause of death, typically occurring between 3 and 5 years after diagnosis[3]. Traditionally, this disease has been thought to primarily present with motor symptoms, though there is a growing body of evidence indicating non-motor symptomatology detected

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in early stages in 80% of patients, which impacts survival in ALS[4]; among those that have been described: cognitive and behavioral deficits[5], autonomic disturbances[6]. and sensory disturbances[7].

It is also worth highlighting among these alterations, deficiencies in both the quantity and quality of sleep, known as sleep disturbances[8]. The sleep disturbances have been diagnosed in over 50% of ALS patients[9], primarily demonstrating decreased total sleep time and sleep efficiency[10], consequently reducing their quality of life[11]. Therefore, it is important to further investigate the variables predicting sleep disturbances in patients with ALS, in which the specific pathophysiological mechanisms related to sleep disturbances are not fully understood, although they are often accompanied by an increase in free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). This elevation in free radicals reduces antioxidant capacity in the blood and in turn promotes immune activation, inflammation, and even greater oxidative stress; variables that interact with each other, increasingly exacerbating sleep abnormalities[12,13]. Specifically, this reduction in antioxidant capacity has been associated in other populations not only with sleep disturbances, but also with the presence of psychological distress based on anxiety and depression[14], which, in turn, are characteristic features of ALS[15].

Other variables, such as age and sex, have been associated with sleep disturbances and may help understand them. There is no sexual predominance of sleep disorders in childhood and adolescence, but sleep disorders occur in middle age, especially in women during pregnancy or menopause[16], leading women to have a higher likelihood of developing anxiety disorders, which are in turn linked to poorer sleep quality[17]. These differences in the sex have been primarily linked to the fact that circadian rhythms in middle age are regulated differently between women and men[18].

Building upon this background, the objective was to determine the predictive role of antioxidant status, psychological distress, age, and sex on sleep deterioration in an adult population of ALS patients.

Methods

Design

A descriptive, quantitative and cross-sectional study was carried out. The clinical trial ID for this study was NCT04654689 (first registration 13/11/2020) (https://clinicaltrials.gov/study/NCT04654689#wrapper).

Participants

A total of the sample consisted of 74 patients with ALS with bulbar- or spinal-onset ALS.

Procedure

Patients were recruited by random sampling through the ALS national associations as part of the clinical trial NCT04654689. Participation in the study was voluntary and anonymous. Participants received information about the study prior to participation and did not receive financial compensation for their involvement. The measurement instruments were completed by the members of the research group. The project was approved by the Ethics Committee of Clinical Research at Hospital la Fe in Valencia, Spain (2021-001989-38), and was conducted in accordance with the Helsinki Declaration[19]. Participants were then assessed against a series of selection criteria. The inclusion criteria were: males over 18 years of age, females over 50 who are not fertile, or between 18 and 50 years old; patients diagnosed with ALS for at least six months prior to the study; patients receiving riluzole treatment; patients who had experienced some type of sleep disturbance during the course of the disease, and those who agreed to participate by signing the informed consent form. The exclusion criteria included: patients with a tracheostomy; patients with invasive or non-invasive ventilation with positive ventilatory pressure; those involved in another trial within 4 weeks prior to inclusion; patients with evidence of dementia; those dependent on alcohol or drugs; patients infected with hepatitis B or C or who are human immunodeficiency virus positive; patients with renal issues indicated by creatinine levels twice the normal limit 30 days before inclusion; and patients with liver issues shown by ALT or AST levels three times the normal limit 30 days before inclusion.

Sleep disturbances determination

The following questionnaires were used to assess sleep disturbances:

- Pittsburgh sleep quality index (PSQI)[20]. Developed by Buysee et al., it assesses the overall quality of sleep in the previous month. It consists of 19 self-assessment questions and seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The frequency of symptoms per week was scored on a scale from 0 to 3. The global PSQI score ranges from 0 to 21, with higher scores indicating poorer sleep quality. In our study, the internal consistency (Cronbach's alpha) was 0.80, exceeding the recommended minimum of 0.70[21].
- Epworth sleepiness scale (ESS)[22]. Johns designed it to assess daytime sleepiness. The ESS is a trait scale that measures the likelihood of falling asleep in 8 everyday situations. Each response is scored on a scale of 0–3. The total ESS score ranges from 0 to 24, with a score above 16 indicating a high level of daytime sleepiness. This scale demonstrated an internal consistency of 0.61, which is slightly lower than expected (0.70) and can be attributed to the small sample size ($n = 74$).
- Insomnia severity index[23]. The Insomnia severity index (ISI), originally known as the Sleep Impairment Index, consists of seven questions that assess the symptoms of insomnia on a 5-point Likert scale. The questions measure the severity of sleep disturbance, sleep satisfaction, daily functioning impairment, the significance of the resulting impairment, and the emotional distress associated with it. ISI scores range from 0 to 28, with higher scores indicating more severe insomnia symptoms. Several thresholds are defined: a score of 0 to 7 is considered normal, while scores of 8, 15, and 22 represent subthreshold, moderate, and severe insomnia,

respectively. This scale demonstrated an internal consistency of 0.85 in our sample, higher than the value of 0.74 obtained in its first validation[24].

Antioxidant capacity (oxidative stress)
Fasting blood samples were collected to determine the antioxidant capacity of the analytes. The samples were centrifuged at 1500 g for 5 min, and the serum was separated and frozen at −80 °C until measurement. The analytes related to antioxidant capacity measured were Trolox equivalent antioxidant capacity (TEAC), Cupric ion reducing antioxidant capacity (CUPRAC) and Ferric reducing power (FRAP). These analytes were measured using an automated biochemical analyser (Olympus AU600, Olympus Europe GmbH, Germany), as described by Rubio et al.[25].

Psychological distress

- ALS depression inventory-12[26]. It consists of 12 items that are designed to assess depression. It was specifically developed for patients with ALS and addresses depressive symptoms, excluding the increasing physical impairments that are characteristic of ALS. The ALS Depression Inventory- 12 considers the mood of the past 2 weeks and uses a four-level response format ("completely agree" to "completely disagree"). Internal consistency was 0.91.
- Beck anxiety inventory (BAI)[27]. The BAI is a 21-item self-report instrument that is designed to assess anxiety. Each item represents an anxiety symptom, and the individual rates the extent to which they have been affected by it during the past week, using a 4-point Likert scale. This scale measured both somatic and affective-cognitive anxiety. The internal consistency of both measures was 0.89 for the somatic measure and 0.91 for the affective-cognitive measure.

The revised ALS Functional Rating Scale (ALSFRS-R) was used to evaluate functionality. It is a sensitive, accurate, and reproducible scale that assesses functional capacity considering the domains of deterioration: bulbar, upper limb, lower limb, and respiratory[28].

Data analysis
First, the distribution of the collected measures was calculated to determine whether they followed a normal distribution using the SPSS V. 21 statistical package. Second, Pearson´s correlations were computed between the different quantitative measures collected using SPSS V. 21. Third, three confirmatory factor analyses were conducted using AMOS V. 23[29] for the oxidative stress measures, psychological distress (anxiety and depression) and the three sleep questionnaires to verify if they theoretically grouped into a latent factor. To assess the fit of the data to the confirmatory models, two types of goodness-of-fit indices were used: (1) Absolute indices, to determine if the theoretical model fits the empirical data: the index $\chi 2/df$[30], whose values below 3 indicate a good fit; the Goodness-of-Fit Index (GFI)[31], with values > 0.95 considered a good fit; the Standardized Root Mean Square (SRMR)[32] and the Root Mean Squared Errors (RMSEA)[33], with values < 0.08 indicating a good fit[21]; and the presence of < 5.0% of standardised residuals greater than 2.58 in absolute value[21,31]; (2) *Incremental indices* were used to compare the obtained model with the null model: the Normed Fit Index (NFI)[30], the Comparative Fit Index (CFI), and the Tucker-Lewis Index (TLI)[35], which, with values > 0.95, indicate a good fit.

Fourth, a predictive model was tested using age, sex, psychological distress and antioxidant capacity to predict sleep impairment in patients with ALS.

It is recommended to have 10 participants per indicator for factor analyses[36], although others suggest only 5 participants per indicator when the distribution is normal[21]. In our case, as we had 74 participants for three to five indicators from the different models tested (50/3 = 26.67, 74/5 = 14.80), we almost accomplish both criteria.

Results
A total of the sample consisted of 74 patients with ALS, who had been diagnosed for an average of 28.28 months (SD = 27.69 months), range between 2 and 148 months. The mean age was 56.51 years (SD = 9.98 years). 63.7% were male. 18.9% of patients presented with ALS de inicio bulbar and 81.1% with ALS de inicio espinal; siendo un 10% Familiar ALS, y un 90% Sporadic ALS. The mean ALSFRS-R was 28.37 (SD = 8.40) with a range of 6–46.

Descriptive analyses
Table 1 shows the descriptive statistics for the different measures collected from the patients with ALS. Skewness values not exceeding 2 and kurtosis values not exceeding 7 in absolute value would indicate a normal distribution of the variable, a requirement for using the maximum likelihood procedure to estimate confirmatory factor and predictive models[37]. All measures exhibited a normal distribution.

Correlations
Table 1 presents the correlations among age, antioxidant power measures, psychological distress and sleep deterioration in patients with ALS. Statistically significant correlations ($|r \geq \pm 0.24|$) are shown in bold font. According to Cohen[38], the effect size of the correlation was considered small for values below 0.10, medium up to 0.30, and large from 0.60 onwards. The effect size reflects the population-level importance of the correlation, meaning that a larger effect size indicates a more significant result at the population level, and therefore, more generalisable findings. Age showed a low negative correlation with the sleep deterioration index (r = -0.24), indicating that older individuals tend to have less sleep impairment. The antioxidant capacity measures show medium-to-high correlations (ranging from 0.42 to 0.86), suggesting that these measures could form a latent factor due to the substantial common variance[21]. Psychological distress measures (anxiety and depression) present

Measure	1	2	3	4	5	6	7	8	9	10
1. Age	1.00									
2. TEAC	−0.10	1.00								
3. CUPRAC	−0.02	**0.86**	1.00							
4. FRAP	0.03	**0.42**	**0.54**	1.00						
5. PSQI	−0.09	−0.16	−0.22	−0.11	1.00					
6. ISI	**−0.24**	**−0.30**	**−0.41**	−0.12	**0.73**	1.00				
7. ESS	−0.02	0.07	−0.01	0.04	**0.33**	**0.25**	1.00			
8. Depression	0.13	−0.02	−0.12	0.01	0.19	0.20	**0.30**	1.00		
9. Somatic anxiety	0.03	−0.08	−0.14	0.04	**0.36**	**0.30**	**0.33**	**0.58**	1.00	
10. Affective anxiety	0.01	−0.08	−0.17	−0.05	**0.36**	**0.26**	**0.25**	**0.52**	**0.85**	1.00
Mean	56.51	1.05	0.73	2.45	12.53	16.18	4.60	9.85	21.01	18.58
SD	9.98	0.13	0.07	0.38	6.29	6.56	3.45	6.73	6.75	6.87
Asymmetry	-0.20	−0.45	0.26	0.66	0.35	0.74	1.17	1.37	1.08	1.09
Kurtosis	0.07	0.08	1.11	−0.05	0.61	0.38	2.54	2.68	1.26	0.81

Table 1. Descriptive statistics, distribution, and pearson correlation of the measures. *CUPRAC* cupric ion reducing antioxidant capacity, *ESS* epworth sleepiness scale, *FRAP* ferric reducing antioxidant power, *ISI* Insomnia severity index, *PSQI* Pittsburgh sleep quality index, *TEAC* trolox equivalent antioxidant capacity. The statistically significant correlations at the 5% level are shown in bold.

high correlations (range from 0.52 to 0.85), so they can be considered latent factors. The sleep deterioration measures also showed medium-to-high correlations (ranging from 0.25 to 0.73), which would also suggest the potential for a latent factor. Additionally, antioxidant capacity measures correlated negatively with the two sleep deterioration measures (r = -0.30 and −0.41), with a medium effect size, indicating that antioxidant capacity may act as a buffer for sleep deterioration. Psychological distress measures present positive correlations with sleep deterioration, thus depression correlates 0.30 and anxiety 0.25 and 0.33. In other words, higher antioxidant capacity is associated with less sleep deterioration in patients with ALS and high psychological distress is associated with greater sleep deterioration.

Confirmatory factor analyses

Due to the high correlations between the antioxidant capacity measures, psychological distress and the sleep deterioration measures, which could form three latent factors, three confirmatory factor analyses were conducted for each group of these measures.

Due to the high correlations between the antioxidant capacity measures and sleep deterioration measures, which could form two latent factors, two confirmatory factor analyses were conducted for each group of these measures.

The estimated model for antioxidant capacity is shown in (Fig. 1a). The model indicators exhibit multivariate normality assessed using the Bollen-Stine bootstrap[39] (p = 0.274) and were therefore estimated using maximum likelihood. The goodness-of-fit indices (Table 2) indicate that the model fits the data perfectly. Furthermore, the factor loadings were above the recommended minimum of |± 0.40[21] with values ranging from 0.54 to 0.99. These results suggest that the three antioxidant capacity measures group perfectly under a latent factor, reflecting the common variance of these measures.

The estimated model for psychological distress is shown in (Fig. 1b). The model indicators exhibited multivariate normality assessed using the Bollen-Stine bootstrap (p = 0.428) and were therefore estimated using maximum likelihood. The goodness-of-fit indices (Table 2) indicated that the model fit the data perfectly. Furthermore, the factor loadings were above the recommended minimum of |± 0.40| with values ranging from 0.61 to 0.94. Therefore, the psychological distress measures can be grouped into latent factors.

The sleep impairment model is shown in (Fig. 1c). Multivariate normality was also obtained using the Bollen-Stine bootstrap procedure (p = 0.935); therefore, the model was estimated using the maximum likelihood. The goodness-of-fit indices indicate perfect fit to the data for all indices (see Table 2). Regarding the factor loadings, only the sleepiness scale is below 0.40, with a value of 0.33. However, given the good fit to the data and that the other two indicators have factor loadings > |± 0.40|, we can assume that the three sleep impairment scales form a latent factor reflecting the common variance, and this will be used in the predictive model presented in the following section.

Predictive model of sleep impairment

Figure 2 shows the tested model designed to predict sleep impairment in ALS patients based on age, sex, psychological distress and antioxidant capacity. The model exhibited multivariate normality, estimated using the Bollen-Stine bootstrap (p = 0.796), and was therefore estimated using maximum likelihood. The goodness-of-fit indices, presented in (Table 2), indicate a very good fit to the data. The only predictors that show correlations are sex and antioxidant capacity. The negative value reflects that men have a higher antioxidant capacity than women, meaning that being male is associated with a protective effect against oxidation in patients with ALS.

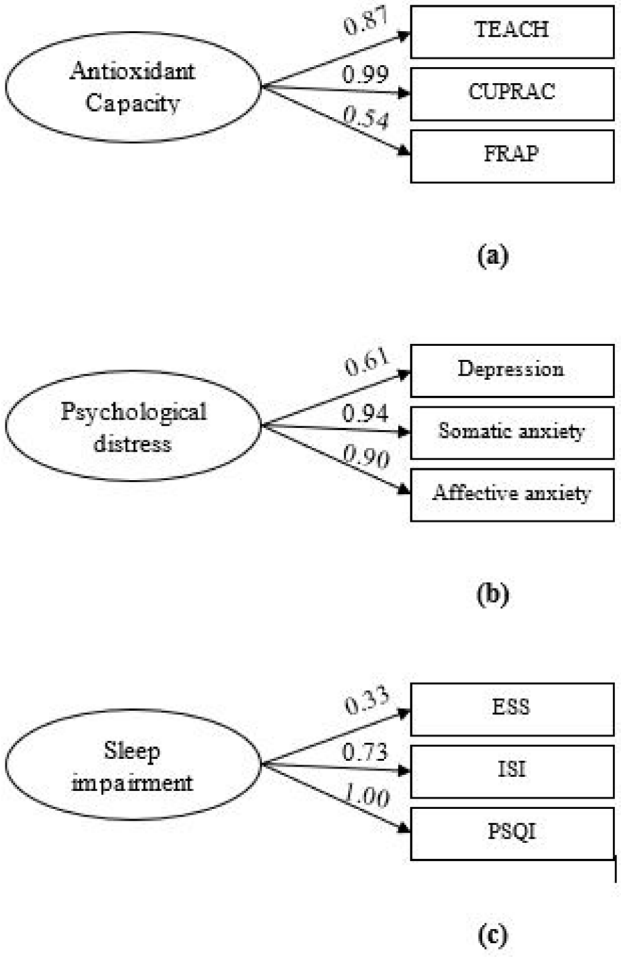

Fig. 1. Confirmatory factor analysis for antioxidant capacity (**a**) psychological distress (**b**) and sleep impairment (**c**) in ALS.

Models	χ^2/df	GFI	NFI	CFI	TLI	RMSEA	SRMR	Residues ≥ |± 2.58| (%)
Antioxidant capacity	1.08	0.991	0.992	0.999	0.998	0.032	0.019	0.00
Sleep Disturbance	0.00	1.000	1.000	1.000	1.000	0.000	0.002	0.00
Psychological distress	0.67	0.994	0.995	1.000	1.000	0.000	0.011	0.00
Predictive model	0.34	0.993	0.975	1.000	1.000	0.000	0.034	0.00

Table 2. Goodness-of-fit indices for the confirmatory factor analyses and the predictive model. *CFI* parsimony comparative fit index, *GFI* goodness of fit index, *NFI* normed fit index, *RMSEA* root mean squared errors, *SRMR* standardized root mean square, *TLI* Tuker- Lewiss index.

Regarding predictors, the model shows linear regression weights. According to Cohen[38], $f^2 = R^2/(1\text{-}R^2)$ value of 0.14 represents a small effect size, 0.36 a medium effect, and 0.51 a large effect. Based on this criterion, age has a medium-low predictive value ($\beta = -0.27$) for sleep quality, meaning that younger individuals have more sleep impairment. Sex has little influence on sleep impairment ($\beta = -0.12$); in any case, men would have more sleep impairment than women. Psychological distress is a positive predictor of the criterion ($\beta = 0.26$), which would indicate that the greater the psychological distress, the greater the deterioration of sleep in ALS patients. Finally, antioxidant capacity shows a medium-high prediction of sleep deterioration ($\beta = -0.43$), indicating that higher antioxidant capacity is associated with less sleep impairment in patients with ALS. Together, these four predictors explain 32% ($R^2 = 0.32$) of the variance in sleep impairment in patients with ALS.

In addition, it can be observed that there is a significant correlation between antioxidant capacity and sex ($r = -0.49$) and psychological distress ($r = -0.12$). These data would indicate that men are the ones who would have more antioxidant capacity and that the antioxidant capacity is able to reduce the psychological distress.

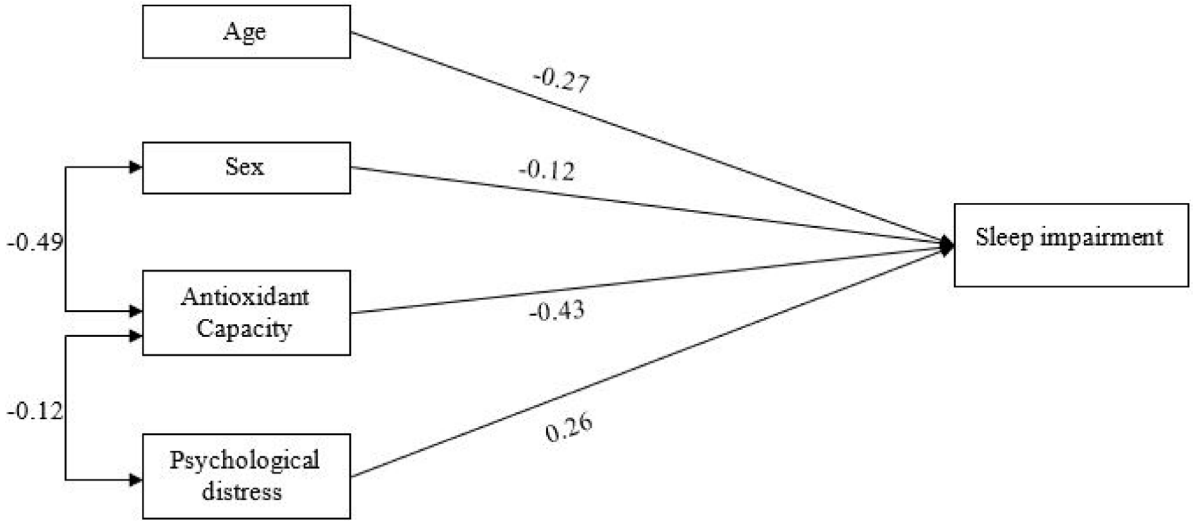

Fig. 2. Predictive model of sleep impairment in ALS patients. Correlations lower than |± 0.15| were removed to simplify the model.

Discussion

The quality and quantity of sleep for an adult are essential to prevent harmful effects on health[40,41], as they are directly linked to the brain's ability to mitigate the accumulation of toxins and proteins in the brain[42]. Specifically, sleep disturbances promote the onset of neurodegenerative diseases, and their relationship with Parkinson's has been extensively studied[43]; or Alzheimer[44]. However, in ALS, sleep disturbances are also observed in most patients[45]. These disturbances are underdiagnosed, underreported, and have not been thoroughly studied. However, it has been shown that they cause a significant loss of quality of life in ALS, which already represents a major issue for the disease[46,47].

In this regard, variables such as age or sex, which are associated with sleep impairment, have also been linked in different ways to the course of the disease, depending on the motor or cognitive phenotype presented by the patients[48]. On the other hand, oxidative stress represents one of the most important etiopathogenic factors in ALS[49]. It has also been linked to sleep disturbance[12]. Therefore, we aimed to establish a predictive model for sleep deterioration in patients with ALS based on these three variables (sex, age, and antioxidant capacity).

Regarding sex, it is important to note that men are 2–3 times more susceptible than women to developing ALS, which is an independent factor that influences the progression of the disease[50]. Additionally, it has been observed that sex influences respiratory disturbances that occur especially during sleep, such as sleep-related respiratory disorders (SRBDs)[51]. In our study, sex did not appear to be a particularly relevant variable, and after analysing the results, we observed that sex has little influence on sleep deterioration, with men seemingly having less deterioration (β =-0.12). These results align with what is observed in the general population, where women report having poorer sleep quality[52], independently of sociodemographic characteristics or lifestyle factors[53], and therefore it does not emerge as a particularly relevant predictor for the disease. However, it is important to consider how sleep disturbances are determined. In our case, as Bonnet et al. began in the previous century, we also assessed the sleep quality of our patients using self-reported questionnaires (PSQI). Despite the sample size (n = 74) and the fact that these tests were designed for a healthy population, two of the tests showed adequate internal consistency (Cronbach's alpha > 0.70), and all three formed a latent factor that measures sleep deterioration with a very good fit to the data (see Fig. 1b). Therefore, we can consider sleep impairment measures reliable and valid in patients with ALS. However, according to Lok et al., self-reported sleep quality does not correlate with objective sleep measures[54]. This aspect should be considered when drawing conclusions, especially given that according to these authors, the relationship between these measures (objective and self-reported) tends to be better in men than in women[55]. On the other hand, age is shown to be an important epidemiological variable for the disease (since only 5% of cases have an onset < 30 years of age, and the majority of cases occur between the ages of 50 and 65, with a median age of onset of 64 years)[2,56]. It is important to note that sleep disturbances are common in aging, with a notable increase in sleep disorders associated with pathological aging[57–59], which is generally associated with a decline in cognitive function[60,61]. Specifically, in other neurodegenerative diseases such as Alzheimer's disease, sleep disturbances are a risk factor that is increased, particularly in women and with aging[44]. However, our results show that older individuals with ALS experience less sleep deterioration (β = -0.26). Therefore, these findings, which have not been reported in any ALS study to date, are particularly interesting, as it seems that an early diagnosis of ALS is associated with worse sleep quality.

Besides, in our study we analysed the influence of antioxidant capacity determined using the TEAC, CUPRAC, and FRAP methods. In this regard, there is limited literature published, but sleep disturbances seem to be associated with higher levels of inflammatory activity, which in turn promotes oxidative stress[12,62]. This association seems to be stronger in women than in men[63]. This could explain our results showing that men have a higher antioxidant capacity than women. Regarding its influence on sleep disturbances, our model seems

to indicate that antioxidant capacity considerably reduces sleep deterioration (β =-0.43); which reinforces the controversial hypothesis that sleep may play an antioxidant role in the brain and peripheral organs[64], a hypothesis that more recent findings seem to validate[65]. This relationship between sleep disturbances and oxidative stress could, in turn, be linked to the increased levels of cannabinoids detected in ALS patients[66], which have been proposed as a compensatory mechanism against inflammation and oxidative stress in the disease[67], and which are also closely related to sleep disturbances[68] Furthermore, it is noteworthy that, in our predictive model, psychological distress is negatively associated with antioxidant capacity (as expected), although to a modest extent (β = -0.12); however, a clear and positive influence is observed between the presence of anxiety and depression and sleep disturbances (β = 0.26), in line with what has been observed in other neurodegenerative diseases such as Alzheimer's[69]. Therefore,, our results appear tooxidative status as an important variable for understanding the pathophysiology of the disease and for the design of new drugs for treating these disturbances.

Considering the objective of our study, we conclude that higher antioxidant capacity (lower oxidative stress), lower psychological distress (anxiety and depression), male sex, and older age seem to be strong predictors of reduced sleep deterioration in ALS. Specifically, these three predictors explain 32% of sleep disturbances.

Despite these results, our study has several limitations. Specifically, as discussed, it would be interesting to complement the information from self-reported questionnaires with more objective measurements of sleep disturbances. It is also important to assess whether different ALS phenotypes influence the results obtained. In this regard, we propose analysing these variables in relation to the functional disability present in patients, which also indicates the progression status of the disease.

In addition to these limitations, it is worth noting the limited access we had in the study to clinical aspects of the population; in this regard, it would have been interesting to have data on the disease progression rate and values such as the King stage, the Modified Medical Research Council Dyspnea Scale (mMRC), and the Penn Upper Motor Neuron Score (PUMNS), which would have complemented all the tests and assessments performed by our experts. It would also have been valuable to know the presence of Spastic Hypertonia and Difficulty in Falling Asleep as well as any additional medications prescribed beyond riluzole (particularly those related to the management of spasticity or mood). Finally, it is also important to highlight that in our study, an analysis of sleep disturbances was conducted based on subjective self-assessments (PSQI, ESS, ISI), without complementary objective sleep measurements (e.g., polysomnography). This limitation is particularly relevant, as ALS patients may experience nocturnal disturbances, such as hypercapnia, long before they report insomnia or nocturnal dyspnea.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
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Informed consent statement
Written informed consent has been obtained from the patients to publish this paper.

Consent to participate
Informed consent was obtained from all individual participants included in the study.

Additional information
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